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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/809,745	03/15/2001	Howard L. Weiner	B0801/7202 (AWS)	5345

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EXAMINER	
LIU, SAMUEL W	
ART UNIT	**PAPER NUMBER**
1653	

DATE MAILED: 10/02/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/809,745	WEINER ET AL.	
	Examiner	Art Unit	
	Samuel W Liu	1653	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *29 May 2001* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-11,19,25,31 and 44* is/are pending in the application.

4a) Of the above claim(s) *44* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-11,19,25 and 31* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Status of the claims

Applicants' preliminary amendment filed 29 May 2001, which cancels claims 12-18, 20-24, 26-30, 32-43 and 45-55, has been entered. Claims 1-11, 19, 25, 31 and 44 are pending.

Election/Restrictions

Applicant's election (see the response filed 22 August 2003) of Group I, claims 1-11, 19 and 31 are acknowledged. Because applicant did not distinctly and specifically point out the supposed errors in the restriction requirement, the election has been treated as an election without traverse (MPEP § 818.03(a)). Therefore, elected claims 1-11, 19 and 31 are under examination to the extent that they are drawn to the elected invention.

Object to IDS

Please note that Applicants' submission of IDS filed 11 June 2002 is incomplete since it contains no copies of each foreign patent and each publication recited in IDS filed 11 June 2001 from rows B11 to B12 and C1 to C36 in the list of the submitted IDS. Thus, it fails to comply with the provisions of 37 CFR 1.97, 1.98 and MPEP § 609. Applicants are advised that the date of any re-submission of any item of information contained in this information disclosure statement or the submission of any missing element(s) will be the date of submission for purposes of determining compliance with the requirements based on the time of filing the statement, including all certification requirements for statements under 37 CFR 1.97(e). See MPEP § 609 ¶ C (1). Yet, examiner has reviewed all US patent documents listed in the IDS by applicants.

Specification Objections

The disclosure is objected to because of the following informalities:

In page 2, line 9, "HSP" of the recitation "HSP65" should be fully spelled out for the first instance of use. See also page 25, line 28, "PBS"; page 26, line 12, "ELISAs", line 16, "BSA", and line 27, OCT"; and page 27, line 20, "CFA".

The disclosure is objected to because it contains an embedded hyperlink and/or other form of browser-executable code in page 13, line 28,. Applicant is required to delete the embedded hyperlink and/or other form of browser-executable code. See MPEP § 608.01.

Appropriate correction is required.

Claim Rejections - 35 USC § 112, the second paragraph

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter that the applicant regards as his invention.

Claims 1-11, 19 and 31 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 1, 11, 19 and 31 recitation of "analog of a heat chock protein" is indefinite because the specification does not define the "analog", and the recitation is unclear as to whether or not the said analog encompasses any non-proteinous molecule, or any protein mimics of HSP. The dependent claims are also rejected.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-7, 11, 19 and 31 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a process of treating a vascular disorder in a mammal comprising administering to a mucosal surface a composition comprising heat shock protein 60 (HSP60) or heat shock protein 65 (HSP65) or a fragment of HSP65 as described in page 11, line 35 to page 12, line 6. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

The application disclosure and claims have been compared per the factors indicated in the decision *in re* Wands 8 USPQ2d 1400, 1400 (Fed. Cir. 1998). These factors are considered when determining whether there is sufficient evidence to support a description that a disclosure does not satisfy the enablement requirement and whether any necessary experimentation is undue. The factors include but not limited to: 1) the nature of the invention; 2) the breath of the claims; 3) the predictability or unpredictability of the art; 4) the amount of direction or guidance presented; 5) the presence or absence of working examples; 6) the quantity of experimentation necessary; 7) the relative skill of those skilled in the art.

Each factor applicable is addressed below on the basis of comparison of the disclosure, the claims and the state of the prior art in the assessment of undue experimentation.

(1) The scope of the claims/(2) The nature of the invention:

Claims 1, 19 and 31 set forth that the composition used in the claimed method comprises a heat shock protein, i.e., any type of HSP molecule. Yet, the specification provides insufficient

description and working examples as to treating a vascular disorder using a composition comprising *any* HSP other than HSP60 or HSP65. Note that HSP encompasses a growing number of proteins including five conserved classes: HSP100, HSP90, HSP70, HSP60 and the small heat-shock proteins (sHSPs) (see Kim, K. K. et al. (1998) *Nature*, 394, 595-599); each class of HSP is both structurally and functionally divergent, e.g., α-crystallin form the vertebrate eye lens is a member of sHSP, while HSP90 per se also can act as a receptor of peroxisome proliferator activated receptor-alpha (see Sumanasekera, W. K. et al. (2003) *Biochemistry*, 42, 10726-10735), and Dnak, a HSP70 member, is a secondary amide peptide bond *cis-trans* isomerase (see Schiene-Fischer, C. et al. (2002) *Nature Struct. Biol.* 9, 419-424). These examples suggest that not all HSP molecules share common biological function(s) as well as their protein structures. The current application does not provide guidance and working examples as to applicability of any the HSP molecules for the claimed method. Thus, the current disclosure is not enabling in use of any HSP molecules other than HSP60 or HSP65. Therefore, the scope of claims is outside the bounds of the enablement and would have resulted in the necessity of undue experimentation.

Also, there is no description in the specification regarding analog of any HSP including HSP60 and HSP65. The analog encompasses non-proteinous molecule, or any protein mimics of the HSP molecule. Applicant has disclosed only use of the fragments of HSP65 (see the bridging pages 11-12); therefore, the skilled artisan cannot envision all the contemplated HSP analog possibilities which are structurally and/or functionally divergent from unmodified HSP molecules, and would not know how to make and use the HSP analog(s) to formulate the composition comprising the analog thereof for treating a vascular disorder.

(3) The unpredictability of the art:

The claimed invention is directed to a vast number of the variant (analog) HSP molecules, which include any mutants (genetically or/and recombinantly or chemically generated), non-proteinous HSP derivatives, or any protein mimics of HSP. The specification provides not teaching or guidance as to how to make, characterize and use the variants thereof. Thus, the skilled artisan would not know how to make, characterize and use the variant HSP. As a result, outcome of the method of treating a vascular disorder comprising administering the composition comprising the HSP variant thereof are unpredictable.

The current claim language "a heat shock protein" represents a genus encompassing any members of five HSP classes (see the statement supra); without guidance or/and working example as to how to use of any type of HSP to treat a vascular disorder, the specification is not enabling.

Applicant has disclosed only use of the fragments of HSP65; therefore, the skilled artisan cannot envision all the contemplated HSP analog possibilities which are structurally and/or functionally divergent from unmodified HSP molecules, and would not know how to make and use the HSP analog(s) to formulate the composition comprising the analog thereof for treating a vascular disorder. Consequently, conception cannot be achieved until a representative description of the structural and functional properties of the claimed invention has occurred, regardless of the complexity or simplicity of the method. Therefore, unpredictability of the claimed method comprising use of a HSP or analog molecule thereof is exceedingly high.

(4) The state of the prior art:

The general knowledge and level of skilled in the art do not supplement the omitted description because specific, not general, guidance is what is needed. Since the disclosure fails to describe common attribute and characteristics that identify any pharmaceutical agent qualified

for treating a vascular disorder. As stated above, the current claim language "a heat shock protein" represents a genus encompassing any members of five HSP classes and "analog" which encompasses any variants of any structural modifications. Because the genus is highly variant, the specification needs to provide sufficient guidance to be considered enabling.

(5) The quantity of experimentation necessary:

In the absence of working examples with regard to the genus stated above, unpredictability of the art, the lack of sufficient guidance in the specification and the breadth of the claims, it would take undue trials and errors to practice the claimed invention. The quantity of experimentation would be large and unpredictable. One skilled in the art would be required to carry out an undue experimentation for screening and characterizing the HSP that is suitable for treating a vascular disorder or HSP analogs that have pharmaceutical activity against vascular disorder state.

(6) The relative skill of those in the art:

The general knowledge and level of skill in the art do not supplement the omitted description with respect to a massive number of variant sequences of peptide. In view of the preceding factors (1-5), the level of skill in this art is high and requires at least a molecular biologist with several years of experience in mutagenesis, protein engineering as well as knowledge in HSP biochemistry, pathology and pharmacology. Yet, even with a level of skill in the art as those mentioned in precedence, predictability of the results is still highly variable. An unduly level of skill is needed for the skilled artisan in order to identify the useful HSP molecule, which is selected from the five HSP classes and functionally characterized for its efficacy of treating a vascular disorder.

In consideration of each of factors stated above, absent factual data to the contrary, the amount and level of experimentation needed is undue.

Claim Rejections - 35 USC §103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1, 3-7, 11, 19 and 31 are rejected under 35 U.S.C. 103(a) as being unpatentable over Srivastava, P. K. et al. (US Pat. No. 6007821) taken with Wick, G. et al. (*Am. Heart J.* (1999) 138, S444-S449).

Srivastava et al. teach a method of treating tissue disrupted by atherosclosis that is a typical vascular disorder state (see abstract and column6, lines 42-46) or treating ischemia that is

a type of vascular disorder (see column 20, lines 45-53) comprising administering the HSP, e.g., gp96, HSP90, to a mammal (see column 21, lines 21-33 and the patent claims 1 and 6), as applied to claims 1 and 7 of the instant application. Since the Srivastava's teaching is directed to tissue repair for the vascular disorder state (e.g., atherosclosis, (see column 2, lines 32-41)) in a mammal (see the patent claim 2), i.e., suppressing the vascular disorder state, as applied to claim 19 of the current application.

Srivastava et al. teach the method of the administering HSP to oral mucosa, intestinal mucosa (see column 18, lines 22-29), as applied to claims 3-4 of the current application.

Srivastava et al. teach the administration rout is carried out by inhalation (see column 19, lines 38-49), as applied to claim 11 of the current application.

Also, Srivastava et al. teach the method comprises oral administration of the HSP to the subject, as applied to claims 31 of the current application.

Srivastava et al. do not explicitly teach the disorder state of the treatment is a cell-mediated immune response.

Wick et al. teach that the vascular disorder, i.e., atherosclosis, is an autoimmune disease atherosclosis. The Wick et al teaching is applicable to the instant claim 5.

It would have been obvious to one of ordinary skill in the art at the time the invention was made to combine the teachings of the above references because Srivastava et al. teach a method of treating disorder states including vascular disorder via promoting tissue repair comprising administering to a patient the pharmaceutical composition comprising HSP, and

teach the treatment of atherosclosis, and Wick et al teach that atherosclosis, associated with a cellular immune response.

One of ordinary skill in the art at the time the invention was made would have readily combined the above reference teachings to make and use the HSP molecule, i.e., member of HSP90 family (see patent claim 1; yet, note that herein HSP is NOT any HSP molecule but rather a specific type of HSPs) to treat a vascular disorder *since* (i) atherosclosis is a multi-factorial disease (see the abstract of Wick et al. reference), and (ii) tissue repair for vascular disorder, atherosclosis, taught by Srivastava et al. is a treatment of the vascular disorder state and because the same composition comprising a HSP, the same administering route and dosage, the same subject of the treatment (taught by Srivastava et al.) would have resulted in indistinguishable pharmaceutical effect (outcome). Thus, using the HSP to treat atherosclosis – a vascular disorder state, would have been inherent in Srivastava et al. patent; when combined, the skilled artisan will be led to expectation of success and arriving at the current invention.

Furthermore, when combined, there would be the advantage of that the use of HSP is not only importance for maintaining cell integrity under normal physiological condition, but also a great need for compositions that promote vascular tissue healing, i.e., treating vascular disorder, as taught by Srivastava et al. (see column 2, lines 36-38 and lines 63-64, and abstract).

Given the above motivation, one of ordinary skill in the art would have combined the teachings of the above references to develop the method for treating vascular disorder comprising administering to a subject a composition comprising the HSP. Therefore, the claimed invention was *prima facie* obvious to make and use the invention at the time it was made.

Conclusion

No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Samuel Wei Liu whose telephone number is (703) 306-3483. The examiner can normally be reached from 9:00 a.m. to 5:00 p.m. on weekdays. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Dr. Christopher Low, can be reached on 703 308-2923. The fax phone number for the organization where this application or proceeding is assigned is 703 308-4242 or 703 872-9306 (official) or 703 872-9307 (after final). Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703 305-4700.

KAREN COCHRANE CARLSON, PH.D
PRIMARY EXAMINER

Samuel W. Liu, Ph.D.

September 12, 2003